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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY.DOCKET NO.	CONFIRMATION NO.
09/273,445	03/19/1999	JAMES K. LIAO	B0801/7137/E	7143

959 7590 12/08/2003

LAHIVE & COCKFIELD, LLP.
28 STATE STREET
BOSTON, MA 02109

EXAMINER	
KIM, JENNIFER M	

ART UNIT	PAPER NUMBER
1617	22

DATE MAILED: 12/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/273,445	Applicant(s) LIAO ET AL.	
	Examiner Jennifer Kim	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *236-342* is/are pending in the application.

4a) Of the above claim(s) *236-248 and 262-342* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *262-275* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *76,7,19* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 236-248 and 316-342, drawn to a method for increasing Nitric Oxide production in a subject administering a HMG-CoA reductase inhibitor, classified in class 514, subclasses 451, 460.

II. Claims 249-261, drawn to a method for attenuating the downregulation of Nitric Oxide production comprising administering a HMG-CoA reductase inhibitor, classified in class 514, subclass 451,460.

III. Claims 262-275, drawn to a method for treating a nonhypercholesterolemic or nonhyperlipidemic subject with a cardiovascular disease or disorder comprising administering a HMG-CoA reductase inhibitor, classified in class 514, subclasses 451, 460.

IV. Claims 276-290, drawn to a method for treating a cerebrovascular disease or disorder comprising administering a HMG-CoA reductase inhibitor, classified in class 514, subclass 451,460.

V. Claims 291-304, drawn to a method for increasing cerebral blood flow in a cerebral tissue comprising administering a HMG-CoA reductase inhibitor, classified in class 514, subclasses 451, 460.

VI. Claims 305-315, drawn to a method for increasing Nitric Oxide Synthase activity in a subject, the method comprising administering a HMG-CoA reductase inhibitor and a Nitric Oxide Synthase substrate, classified in class 514, subclass 451, 460, 565.

VII. Claims 328-342, drawn to a method for treating an inflammatory disease or disorder comprising administering a HMG-CoA reductase inhibitor, classified in class 514, subclasses 451, 460.

The inventions are distinct, each from the other because of the following reasons:

Inventions Group I and II-VII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different effect since each inventions above are related to different and independent disorders, which have different etiology. Moreover, the disorders in each invention are known to treat differently with unrelated active agents.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

Claims 236, 262, 276, 291, 305, 316 and 328 are generic to a plurality of disclosed patentably distinct species comprising various HMG-CoA reductase inhibitors.

Applicants are required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

Should applicants traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

During a telephone conversation with Ms. Herritt on November 12, 2003 a provisional election was made without traverse to prosecute the invention of Group III, claims 262-275 with simvastatin as a species election. Affirmation of this election must be made by applicant in replying to this Office action. Claims 236-248, 262-342 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicants are reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Applicants' election without traverse of Group III, claims 262-275 drawn to a method for treating a nonhypercholesterolemic or nonhyperlipidemic subject with a cardiovascular disease or disorder, comprising administering a HMG-CoA reductase inhibitor with elected species as Simvastatin is acknowledged. Accordingly, claims 236-248 and 262-342 are withdrawn from consideration since they are non-elected inventions. Claims 262-275 have been examined only to the extent of applicants' election.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 262-267, 269, 270, 271 and 273 are rejected under 35 U.S.C. 102(e) as being anticipated by Kaesemeyer (U.S.Patent No. 6,465,516B1) of record.

Kaesemeyer teaches a method for treating pulmonary hypertension, unstable angina, myocardial infarction and cariomyopathy, irrespective of the subject's cholesterol level or nonhyperlipidemic comprising administering HMG-CoA reductase inhibitor including simvastatin. (column 5, lines 1-33, column 10, claims 1-14). Kaesemeyer teaches that HMG-Co-A reductase and L-arginine can be combined in a mixture and they may have an unexpected synergistic effect. (column 7, lines 23-45, column 6, lines 8-10). Kaesemeyer teaches that above formulation can be administered as IV (injectable). (column 6, line 30).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 268, 269 (limitations directed to capsules, tablets and lozenge), 272 and 273 (limitations directed to capsules, tablets and lozenge) are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaesemeyer (U.S.Patent No. 6,465,516B1) of record as applied to claims 262-267, 269, 270, 271 and 273 above, and further in view of Dansereau et al. (U.S.Patent No. 5,622,721).

Kaesemeyer as applied as before and additional teachings as follow:

Kaesemeyer teaches that above composition can be administered orally. (column 6, lines 9-31, particularly, line 30).

Kaesemeyer does not teach the specific delivery system set forth in claims 268 and 272, and the specified oral formulations set forth in claim 269 and 270.

Dansereau et al. teach that sustained-release and delayed release formulations and the dosage formulated in tablets or capsules set forth in Applicants' claims 268, 269, 272, and 270 are well known to those skilled in the art. (column 5, lines 53-59).

It would have been obvious to one of ordinary skill in the art to formulate Kaesemyer's composition to formulate in the formulation well-known to the skilled in the art such as sustained-release and delayed release capsules or tablets because Kaesemeyer teaches that the composition above can be administered orally and because the formulations such as sustained-release tablets and capsules are well-known by those skilled in the art by Dansereau et al.

Absent any evidence to contrary, there would have been reasonable expectation of successfully formulating Kaesemeyer's oral composition to well-known formulations of sustained release tablets or capsules to achieve expected benefit of conveniently administering less frequent dosage regimen to save time.

Claims 274 and 275 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaesemeyer (U.S.Patent No. 6,465,516B1) of record as applied to claims 262-267, 269, 270, 271 and 273 above, and further in view of Birkmayer (U.S.Patent No. 5,668,114)

Kaesemeyer as applied as before.

Kaesemeyer does not teach the nitric oxide synthase cofactors set forth in claims 274 and 275.

Birkmayer teaches that NADPH is useful for the treatment of hypertension. (abstract).

It would have been obvious to one of ordinary skill in the art to combine NADPH to Kaesemeyer's composition because NADPH is useful for the treatment of

hypertension. One would have been motivated to make such a modification to achieve at least an additive effect in treatment of hypertension. Absent any evidence to contrary, there would have been a reasonable expectation of successfully treating cardiovascular disease (e.g. hypertension) of patients disclosed by Kaesemeyer.

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 703-308-2232. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 703-305-1877. The fax phone number for the organization where this application or proceeding is assigned is 703-308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Sreenivasan Padmanabhan
Supervisory Examiner

12/1/03

Art Unit 1617

Jmk
November 25, 2003